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Prognostic value of maternal N-terminal pro-B-type natriuretic peptide for prediction of severe maternal adverse outcome in women with pre-eclampsia

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KEYWORDS: angiogenic marker; cardiovascular biomarker; NT-proBNP; pre-eclampsia

ABSTRACT

Objective *N-terminal pro-B-type natriuretic peptide (NT-proBNP), a marker of cardiac stress, has been proposed as a potential prognostic biomarker for maternal adverse outcome in pre-eclampsia (PE). This study aimed to evaluate the predictive value of NT-proBNP for severe maternal adverse outcome in pregnancies with an established diagnosis of PE.*

Methods *This was a retrospective cohort study of singleton pregnancies diagnosed with PE ≤ 36 weeks of gestation that were assessed at the Medical University of Vienna between January 2018 and December 2023. Maternal serum levels of NT-proBNP, soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) were measured at the time of PE diagnosis. The primary outcome was the occurrence of a severe maternal adverse event, including intensive care unit admission, maternal death, pulmonary edema and severe neurological complications. Associations between severe maternal adverse outcome and Z-scores for NT-proBNP and the sFlt-1/PlGF ratio were analyzed using logistic and Cox regression models adjusted for gestational age at sampling and the Z-score of the other biomarker. The area under the receiver-operating-characteristics (ROC) curve (AUC) was used to assess the discriminative ability of the biomarkers.*

Results *Of 130 women included in our cohort, 13 (10%) experienced severe maternal adverse outcome. NT-proBNP levels were significantly higher in this group (median, 688.0 (interquartile range (IQR), 249.6–1038.0) pg/mL* vs *106.1 (IQR, 50.6–280.6) pg/mL; P < 0.001). Higher NT-proBNP Z-score was associated significantly with severe maternal adverse outcome (adjusted odds ratio, 3.24 (95% CI, 1.50–7.84); P = 0.005) and predicted shorter time-to-delivery with severe maternal adverse outcome (adjusted hazard ratio, 3.08 (95% CI, 1.47–6.44); P = 0.003) after adjusting for gestational age at sampling and sFlt-1/PlGF ratio Z-score. The sFlt-1/PlGF ratio was not associated significantly with these outcomes. ROC-curve analysis showed that NT-proBNP had superior discriminative performance compared with the sFlt-1/PlGF ratio (AUC, 0.75 (95% CI, 0.61–0.90)* vs *0.67 (95% CI, 0.56–0.79)). The performance of both biomarkers improved when combined with gestational age at sampling (AUC, 0.82 (95% CI, 0.71–0.94)* vs *0.76 (95% CI, 0.65–0.88)).*

Conclusion *NT-proBNP was a strong predictor of severe maternal adverse outcome and time-to-delivery in women diagnosed with PE, especially in early-onset cases. NT-proBNP may serve as a clinically accessible biomarker for risk stratification and surveillance in women with established PE.* © *2025 The Author(s). Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Pre-eclampsia (PE) affects 2–5% of pregnancies worldwide and remains a leading cause of maternal and neonatal morbidity and mortality[1,2]. Pregnancy induces substantial physiological changes that place significant stress on the cardiovascular system[3]. These changes include increased cardiac output and heart rate, along with decreased blood pressure and peripheral vascular resistance[3].

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Cardiovascular adaptation to pregnancy is impaired in PE, with diastolic dysfunction being a common manifestation of this maladaptation[4]. PE is hypothesized to result from inadequate cardiac reserve or excessive cardiovascular demand, leading to placental dysfunction. This is associated with increased levels of antiangiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1), and reduced expression of angiogenic placental growth factor (PlGF)[5,6]. sFlt-1, PlGF and their ratio have been studied extensively for PE prediction and diagnosis[7–10], showing superior accuracy for predicting adverse outcome and time-to-delivery interval compared with conventional methods[11–15].

Pregnancies affected by PE often exhibit reduced cardiac output, elevated systemic vascular resistance and left ventricular diastolic dysfunction, especially in cases of early-onset PE[4,16–19]. These cardiovascular changes induce cardiac myocytes to release markers of cardiac damage[20]. N-terminal pro-B-type natriuretic peptide (NT-proBNP), which is produced primarily by ventricular cardiomyocytes in response to volume or pressure overload[21], is a well-established marker of heart failure in the non-pregnant population[22,23]. Elevated NT-proBNP has been reported in hypertensive disorders of pregnancy (HDP), reflecting left ventricular diastolic dysfunction[20,24–26]. Recent studies investigating the role of NT-proBNP as a marker for the prediction of PE revealed promising results, particularly when used in combination with other biomarkers[20,26]. Garrido-Giménez *et al.* demonstrated superior predictive performance using NT-proBNP, the sFlt-1/PlGF ratio and uric acid compared with the sFlt-1/PlGF ratio alone for ruling in and ruling out preterm PE in women with clinical suspicion of PE[20].

Álvarez-Fernández *et al.* showed that women who developed PE later in pregnancy had increased levels of NT-proBNP compared with non-PE pregnancies[27]. The changes in serum NT-proBNP levels were found to be more pronounced in early-onset PE[27,28]. Nan *et al.* reported that maternal serum NT-proBNP had comparable performance to the sFlt-1/PlGF ratio in diagnosing early-onset PE within 1 week after assessment in pregnancies with suspected PE[29]. Moreover, NT-proBNP showed equivalent predictive performance to the sFlt-1/PlGF ratio for PE-related complications, including fetal growth restriction (FGR), stillbirth and placental abruption, within 1 week after sampling[29]. Furthermore, NT-proBNP levels were correlated significantly with time-to-delivery with PE, particularly in women with onset of symptoms before 34 weeks of gestation[27]. It was also shown that, when the sFlt-1/PlGF ratio exceeded 38, adding NT-proBNP improved short-term prediction of delivery due to PE compared with the sFlt-1/PlGF ratio alone[27].

However, the performance of NT-proBNP to predict severe maternal adverse outcomes, particularly cardiovascular events, in women with established PE has yet to be assessed. We hypothesized that NT-proBNP could be a useful marker for surveillance of women with PE and prediction of maternal cardiovascular complications. This study aimed to evaluate the performance of NT-proBNP in predicting maternal adverse outcome after a diagnosis of PE.

METHODS

This was a retrospective cohort study of singleton pregnancies diagnosed with PE ≤ 36 weeks of gestation that underwent assessment of serum NT-proBNP at the time of PE diagnosis at the Medical University of Vienna, Vienna, Austria, between January 2018 and December 2023.

PE was defined according to the practice guidelines of the International Society for the Study of Hypertension in Pregnancy as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or worsening of pre-existing hypertension and additional end-organ manifestation, including proteinuria (protein/creatinine ratio ≥ 30 mg/mmol or ≥ 300 mg protein/24 h), liver involvement (e.g. alanine transaminase or aspartate aminotransferase > 40 IU/L), thrombocytopenia (platelet count < 150 000/μL), kidney dysfunction (serum creatinine > 1 mg/dL), neurological complications (e.g. altered mental state, severe headache, persistent visual scotoma, eclampsia), pulmonary edema or uteroplacental dysfunction (defined as FGR)[30]. Women suffering from a congenital heart defect or other chronic cardiac disease, those with chronic kidney disease and pregnancies with aneuploidy, genetic syndrome or major structural fetal anomaly were excluded.

As part of routine assessment in women with PE, blood samples were taken by venipuncture and stored in a collection tube without anticoagulants to analyze maternal serum levels of NT-proBNP, as well as sFlt-1, PlGF and their ratio. sFlt-1 and PlGF concentrations were assessed using commercially available, fully automated assays on the Elecsys platform (Roche Diagnostics, Penzberg, Germany). NT-proBNP levels were assessed by quantitative *in-vitro* testing based on electrochemiluminescence immunoassays. Analyses were undertaken by biomedical technicians.

We investigated the association of NT-proBNP with severe maternal adverse outcome, focusing on cardiovascular complications and time-to-delivery interval in women with an established diagnosis of PE. Severe maternal adverse outcome was defined as intensive care unit admission, maternal death, pulmonary edema or severe neurological complications (including eclampsia).

Continuous variables are presented as median (interquartile range (IQR)), while categorical variables are presented as *n* (%). Baseline characteristics and biomarker *Z*-scores were compared between patients with and without severe maternal adverse outcome, using the Wilcoxon rank-sum test for continuous variables and the chi-square test or Fisher's exact test, as appropriate, for categorical variables. Gestational age (GA)-adjusted *Z*-scores for the sFlt-1/PlGF ratio and NT-proBNP were calculated using generalized additive models for location, scale and shape (GAMLSS). The GAMLSS model for sFlt-1/PlGF

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ratio used natural splines for GA and assumed an exponential distribution, while the model for NT-proBNP included linear terms for GA for multiple distribution parameters and assumed a generalized inverse Gaussian (GIG) distribution. Relationships between *Z*-scores of the sFlt-1/PlGF ratio and NT-proBNP, and severe maternal adverse outcome were visualized using violin plots with embedded box-and-whisker plots, as well as plots of predicted probabilities from regression models. Multivariable Cox proportional hazards regression was used to assess the association between biomarker *Z*-scores and time-to-delivery in days with severe complications. Model fit was assessed using Nagelkerke's R^2. A multivariable logistic regression model was fitted to evaluate the association between biomarker *Z*-scores and the development of severe complications. Model fit was assessed using Tjur's R^2[31]. Receiver-operating-characteristics (ROC) curve analysis was performed to evaluate the discriminative ability of biomarkers alone and in combination with GA at sampling for predicting severe maternal adverse outcome. The area under the ROC curve (AUC) and 95% CIs were calculated using the DeLong method. Reference percentiles for biomarker values across GAs were derived by calculating *Z*-scores based on the study population, with percentiles corresponding to standard normal distribution values. $P < 0.05$ indicated statistical significance. Statistical analysis was performed using R software (R Foundation for Statistical Computing Platform, Vienna, Austria).

RESULTS

Baseline characteristics and pregnancy outcome

A total of 130 singleton pregnancies with an established diagnosis of PE underwent laboratory assessment of NT-proBNP. Thirteen (10%) women experienced severe maternal adverse outcome. Baseline characteristics and pregnancy outcome are summarized in Table 1. GA at sampling was significantly lower in women who experienced severe maternal adverse outcome compared to those who did not (median, 26.9 (IQR, 25.3–28.6) weeks *vs* 31.3 (IQR, 26.7–34.1) weeks; $P = 0.033$). GA at delivery was also significantly lower in the adverse outcome group (median, 27.6 (IQR, 25.3–28.9) weeks *vs* 33.4 (IQR, 28.3–35.3) weeks; $P = 0.006$). There was no significant difference in mode of delivery between the two groups ($P = 0.796$). Delivery was performed for PE-related reasons in the majority of patients in both groups (85.5% of women without severe maternal adverse outcome and 92.3% of those with severe maternal adverse outcome; $P = 0.800$). In the group of women who experienced severe maternal complications, the majority (69.2%) were delivered for worsening of maternal condition.

Table 1 Baseline characteristics and pregnancy outcome for 130 women with pre-eclampsia, according to whether they developed severe maternal adverse outcome

Parameter	*No severe maternal adverse outcome* (n = *117*)	*Severe maternal adverse outcome* (n = *13*)	P
Maternal age (years)	34.0 (30.0–38.0)	33.0 (29.0–39.0)	0.613
GA at sampling (weeks)	31.3 (26.7–34.1)	26.9 (25.3–28.6)	0.033
SBP at sampling (mmHg)	150.0 (140.0–163.0)	157.0 (146.0–176.0)	0.072
DBP at sampling (mmHg)	95.0 (90.0–104.0)	96.0 (91.0–99.0)	0.981
Nulliparous	39 (33.3)	9 (69.2)	0.025
Mode of conception			0.796
Spontaneous	12/113 (10.6)	1/12 (8.3)	
Ovulation stimulation	1/113 (0.9)	0/12 (0)	
In-vitro fertilization	91/113 (80.5)	9/12 (75.0)	
Egg cell donation	9/113 (8.0)	2/12 (16.7)	
Smoker	9 (7.7)	2 (15.4)	0.674
BMI at presentation (kg/m^2)	27.0 (23.4–32.7)	31.6 (28.8–39.0)	0.153
FGR	69 (59.0)	10 (76.9)	0.338
SGA	8 (6.8)	0 (0)	0.715
Placental abruption	6 (5.1)	1 (7.7)	1.000
GA at delivery (weeks)	33.4 (28.3–35.3)	27.6 (25.3–28.9)	0.006
Mode of delivery			0.796
SVD	12 (10.3)	1 (7.7)	
Ventouse	1 (0.9)	0 (0)	
Primary CS	91 (77.8)	9 (69.2)	
Secondary CS	9 (7.7)	2 (15.4)	
Emergency CS	4 (3.4)	1 (7.7)	
Birth weight (g)	1635.0 (910.0–2116.0)	755.0 (545.0–960.0)	0.005
Birth-weight percentile	12.0 (5.0–27.0)	10.0 (7.0–13.0)	0.608
Apgar score at 5 min	9.0 (9.0–10.0)	9.0 (9.0–9.0)	0.299
NICU admission	74/116 (63.8)	11 (84.6)	0.304

Data are given as median (interquartile range), *n* (%) or *n*/*N* (%). BMI, body mass index; CS, Cesarean section; DBP, diastolic blood pressure; FGR, fetal growth restriction; GA, gestational age; NICU, neonatal intensive care unit; SBP, systolic blood pressure; SGA, small-for-gestational age; SVD, spontaneous vaginal delivery.

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Rates of small-for-gestational age and FGR did not differ significantly between groups ($P = 0.715$ and $P = 0.338$, respectively).

Biomarker characteristics

Women who developed severe maternal adverse outcomes demonstrated significantly elevated levels of NT-proBNP (median, 688.0 (IQR, 249.6–1038.0) pg/mL) compared to women without severe complications (median, 106.1 (IQR, 50.6–280.6) pg/mL; $P < 0.001$) (Table 2). When converted to standardized *Z*-scores to account for GA-related variation, a significant difference persisted between groups (median, 1.1 (IQR, 0.3–1.5) *vs* −0.1 (IQR, −0.6 to 0.5); $P = 0.001$). The sFlt-1/PlGF ratio *Z*-score showed a smaller but still significant difference between groups (median, 0.6 (IQR, 0.2–0.7) *vs* 0.1 (IQR, −0.6 to 0.7); $P = 0.035$).

The distribution of biomarker *Z*-scores stratified by maternal outcome status is illustrated in the form of violin plots with embedded box-and-whisker plots in Figure 1. There is clear separation between outcome groups, with women who experienced severe maternal adverse outcomes showing higher median values for both biomarkers. While there is some overlap in distribution between groups, particularly for NT-proBNP, the overall pattern strongly supports the discriminatory potential of these biomarkers.

Association between NT-proBNP and severe maternal adverse outcome

On multivariable logistic regression analysis adjusted for GA at sampling and sFlt-1/PlGF ratio *Z*-score, NT-proBNP *Z*-score was associated significantly with severe maternal adverse outcome (adjusted odds ratio (aOR), 3.24 (95% CI, 1.50–7.84); $P = 0.005$) (Table 3). In contrast, the sFlt-1/PlGF ratio *Z*-score did not show a significant association with severe maternal adverse outcome after adjusting for GA at sampling and NT-proBNP *Z*-score (aOR, 1.20 (95% CI, 0.52–2.98); $P = 0.684$). GA at sampling adjusted for the *Z*-scores of sFlt-1/PlGF ratio and NT-proBNP was associated inversely with severe maternal adverse outcome (aOR, 0.82 (95% CI, 0.67–0.96); $P = 0.024$), indicating that earlier presentation was associated with higher risk.

On multivariable Cox regression analysis adjusted for GA at sampling and sFlt-1/PlGF ratio *Z*-score, NT-proBNP *Z*-score remained significantly associated with time-to-delivery with severe maternal adverse outcome (adjusted hazard ratio (aHR), 3.08 (95% CI, 1.47–6.44); $P = 0.003$) (Table 4). The sFlt-1/PlGF ratio *Z*-score adjusted for GA at sampling and NT-proBNP *Z*-score showed a positive association with severe maternal adverse outcome (aHR, 2.25 (95% CI, 0.73–6.99)), but this did not reach statistical significance ($P = 0.159$). Figure 2 illustrates the relationship between biomarker *Z*-scores and the probability of severe maternal adverse outcome, stratified by GA at onset of PE. The regression model used to generate these predicted probabilities included an interaction term between GA and biomarker *Z*-scores, allowing the effect of biomarker levels to vary across different GAs. We observed a clear relationship between increased NT-proBNP level and an increased probability of severe maternal adverse outcome, controlling for sFlt-1/PlGF ratio *Z*-score, particularly in early-onset PE cases (≤ 28 weeks of gestation), in which the probability increased from approximately 12.5% at a *Z*-score of 0 to nearly 80% at a *Z*-score of 3. This association remained consistent across GA categories but was weaker in later gestations. In contrast, the sFlt-1/PlGF ratio adjusted for NT-proBNP Z-score showed a weaker association with severe maternal adverse outcome across all GA groups, with probability curves demonstrating a less steep incline.

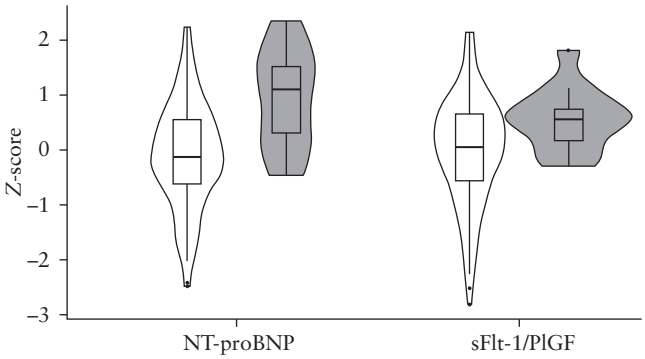

Figure 1 Violin plots with embedded box-and-whiskers plots showing the distribution of *Z*-scores for N-terminal pro-B-type natriuretic peptide (NT-proBNP) and soluble fms-like tyrosine kinase-1 to placental growth factor (sFlt-1/PlGF) ratio in pre-eclamptic patients with (■) and those without (□) severe maternal adverse outcome. Boxes represent median and interquartile range (IQR), whiskers are 1.5 × IQR and circles are outliers. Violin plots represent the probability density of data across *Z*-score values.

Table 2 Serum biomarkers in 130 women with pre-eclampsia, according to whether they developed severe maternal adverse outcome

Parameter	*No severe maternal adverse outcome* (n = *117*)	*Severe maternal adverse outcome* (n = *13*)	P
sFlt-1/PlGF ratio	165.2 (80.0–335.8)	374.9 (217.9–478.2)	0.002
NT-proBNP (pg/mL)	106.1 (50.6–280.6)	688.0 (249.6–1038.0)	< 0.001
sFlt-1/PlGF ratio *Z*-score	0.1 (−0.6 to 0.7)	0.6 (0.2–0.7)	0.035
NT-proBNP *Z*-score	−0.1 (−0.6 to 0.5)	1.1 (0.3–1.5)	0.001

Data are given as median (interquartile range). NT-proBNP, N-terminal pro-B-type natriuretic peptide; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

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On ROC-curve analysis, NT-proBNP had good predictive value, with an AUC of 0.7545 (95% CI, 0.6134–0.8957). The addition of GA at sampling improved the discriminative ability (AUC, 0.8233 (95% CI, 0.7071–0.9394)). For reference, the predictive value of the sFlt-1/PlGF ratio alone was weaker, with an AUC of 0.6733 (95% CI, 0.5582–0.7883), which was improved by the addition of GA at sampling (AUC, 0.7639 (95% CI, 0.6491–0.8787)).

Table 3 Multivariable logistic regression analysis of association between serum biomarkers adjusted for gestational age (GA) at sampling and occurrence of severe maternal adverse outcome

Predictor	*aOR (95% CI)*	P
Intercept	20.34 (0.18–3485.96)	0.221
sFlt-1/PlGF ratio *Z*-score	1.20 (0.52–2.98)	0.684
NT-proBNP *Z*-score	3.24 (1.50–7.84)	0.005
GA at sampling*	0.82 (0.67–0.96)	0.024

Observations, $n = 130$; Tjur's R^2, 0.193. *Adjusted odds ratio (aOR) calculated per 1-week increase in GA. NT-proBNP, N-terminal pro-B-type natriuretic peptide; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

Table 4 Multivariable Cox regression analysis of association between serum biomarkers adjusted for gestational age at sampling and time-to-delivery with severe maternal adverse outcome

Predictor	*aHR (95% CI)*	P
sFlt-1/PlGF ratio *Z*-score	2.25 (0.73–6.99)	0.159
NT-proBNP *Z*-score	3.08 (1.47–6.44)	0.003

Observations, $n = 130$; Nagelkerke's R^2, 0.494. aHR, adjusted hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

Reference values for biomarkers across gestational age

Reference percentiles for NT-proBNP and sFlt-1/PlGF ratio values across GAs are provided in Tables S1 and S2, respectively. These tables present the 2.5th, 10th, 25th, 50th, 75th, 90th and 97.5th percentiles corresponding to *Z*-scores of −1.96, −1.28, −0.67, 0, 0.67, 1.28 and 1.96, respectively, for each week of gestation from 24 to 36 weeks.

DISCUSSION

Summary of key findings

In our study of 130 singleton pregnancies with an established diagnosis of PE, we observed that women who developed severe maternal adverse outcome had significantly elevated levels of NT-proBNP compared to those without severe complications. Our findings suggest a potential association between NT-proBNP levels and the risk of severe maternal adverse outcome, indicating that NT-proBNP may have predictive value for identifying women at increased risk of severe maternal adverse outcome in the context of PE. On multivariable regression analysis, NT-proBNP was associated with the occurrence of, and time-to-delivery with, severe maternal adverse

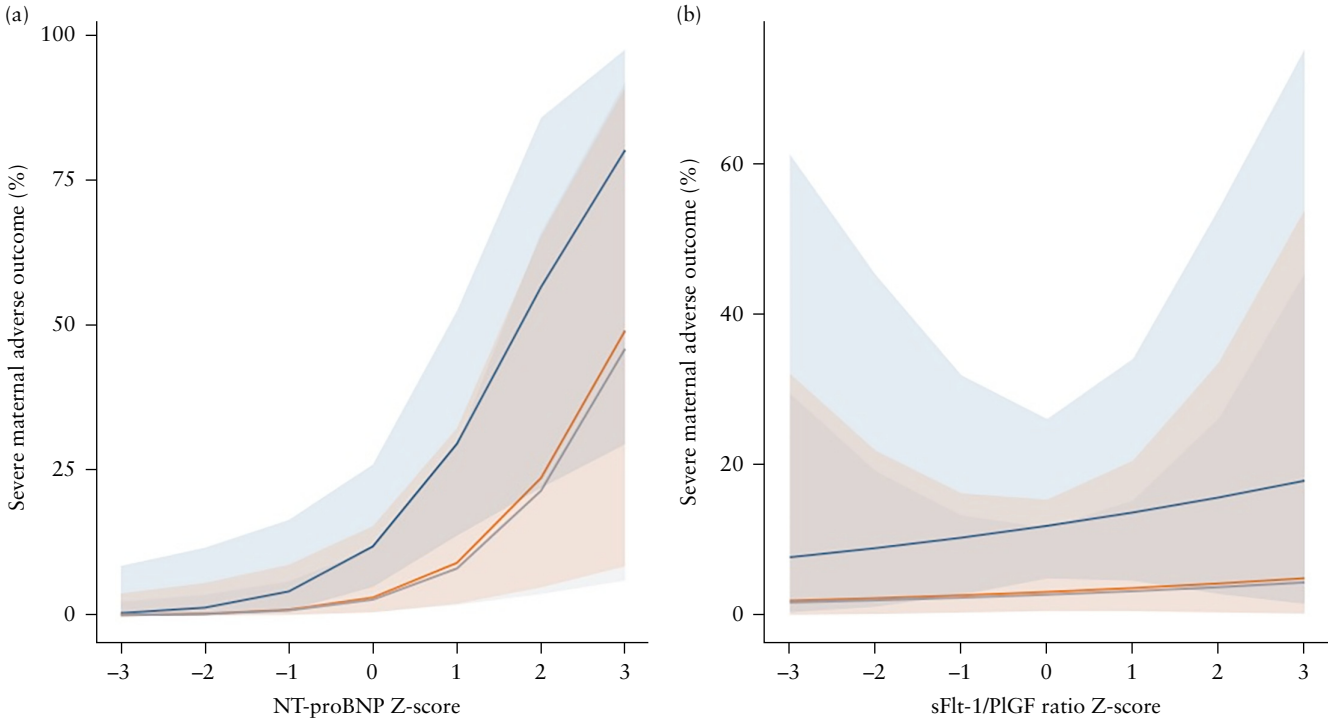

Figure 2 Association of *Z*-scores for N-terminal pro-B-type natriuretic peptide (NT-proBNP) (a) and soluble fms-like tyrosine kinase-1 to placental growth factor (sFlt-1/PlGF) ratio (b) with probability of severe maternal adverse outcome, stratified by gestational age at onset of pre-eclampsia: ≤ 28 weeks (——), > 28 to ≤ 32 weeks (——) and > 32 to ≤ 36 weeks (——). Shaded areas represent 95% CIs.

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outcome, while the well-established sFlt-1/PlGF ratio did not show a significant association with either outcome. The association between NT-proBNP and severe maternal adverse outcome was strongest in early-onset PE cases.

Interpretation and comparison with existing literature

PE is thought to result from an imbalance between maternal cardiovascular reserve and the physiological demands of pregnancy, leading to impaired cardiac adaptation[4]. This may contribute to placental dysfunction and is associated with heightened angiogenic imbalance[5,6]. Recent findings from Papastefanou *et al.*[32] highlight a dynamic interplay between placental angiogenic factors and maternal cardiac function as early as midgestation. Their study demonstrated that lower PlGF level and higher sFlt-1/PlGF ratio were associated with subclinical cardiac dysfunction and hemodynamic changes, independent of pre-existing risk factors. This evidence supports the existence of a close interaction between the placental and cardiovascular systems, further justifying the importance of assessing maternal cardiovascular function in pregnancies with HDP[32].

Measuring NT-proBNP, a biomarker for heart failure and diastolic dysfunction, has been proposed to help identify women at high risk for complications, including cardiovascular events or preterm delivery, although the appropriate cut-off levels for this purpose remain uncertain[27,33]. Serum NT-proBNP levels >136 pg/mL were found to have a high positive predictive value for delivery with PE within 10 days after assessment[26]. In the non-pregnant population, serum NT-proBNP <125 pg/mL is used as a cut-off to rule out heart failure[34]. Álvarez-Fernández *et al.* reported that a cut-off of 219 pg/mL could predict the development of perinatal adverse outcome with a sensitivity of 94% and a specificity of 76% in women with suspected PE[27]. A study by Seong *et al.* showed significantly higher levels of NT-proBNP in women with PE presenting with pulmonary edema or pleural effusion compared to those with normal chest radiography, suggesting an association between NT-proBNP level and disease severity[35]. Furthermore, a recent prospective case–control study by Nan *et al.*, which investigated angiogenic and cardiovascular biomarkers in women with suspected PE, demonstrated strong performance of maternal serum NT-proBNP, which was comparable to that of the sFlt-1/PlGF ratio for predicting the occurrence of early-onset PE within 1 week after assessment[29]. They also showed that a cut-off value of 116 pg/mL for maternal serum NT-proBNP was similarly effective in predicting PE-related fetal complications[29].

In contrast to previous work, our study evaluated the predictive performance of NT-proBNP for severe maternal adverse outcome, with a focus on cardiovascular complications, in women with confirmed PE, and compared its performance with that of the sFlt-1/PlGF ratio. A clear relationship was observed between elevated NT-proBNP level and increased probability of maternal adverse outcome, particularly in cases with early-onset PE ≤ 28 weeks of gestation. This association persisted across GA categories but was weaker in later gestations. This is in line with previous studies showing more pronounced changes in NT-proBNP level in early-onset PE[27,28,36].

Several studies have shown that the angiogenic markers sFlt-1 and PlGF, and particularly their ratio, can improve the prediction of adverse outcome and time-to-delivery interval in pregnancies affected by PE compared with conventional diagnostic methods[11–15,37,38]. The sFlt-1/PlGF ratio is acknowledged as a valuable additive tool to predict maternal adverse outcome in pregnancies with PE[37]. However, Garrido-Giménez *et al.* demonstrated that combining NT-proBNP, sFlt-1/PlGF ratio and uric acid yielded superior predictive performance compared with the sFlt-1/PlGF ratio alone for both ruling in and ruling out preterm PE in women with clinical suspicion of the disease[20]. Similarly, Binder *et al.* showed that the performance of the sFlt-1/PlGF ratio alone was inferior to that of a combination of maternal serum lactate dehydrogenase, creatinine and the sFlt-1/PlGF ratio for the prediction of maternal adverse outcome in women with confirmed PE[37]. Our data show that the sFlt-1/PlGF ratio had a weaker association with severe maternal adverse outcome across all GAs compared with the cardiovascular biomarker NT-proBNP. The best performance for predicting severe maternal adverse outcome was observed with NT-proBNP in early-onset PE cases. In our cohort, NT-proBNP was associated significantly with time-to-delivery with severe maternal adverse outcome. Our findings suggest that NT-proBNP is reflective of maternal end-organ dysfunction in terms of cardiac function, and that it may serve as a more reliable predictor of severe maternal complications related to cardiac end-organ dysfunction in women with PE compared to the sFlt-1/PlGF ratio. This is in line with the study of Zheng *et al.*, in which serum NT-proBNP proved to be an effective marker for assessing PE, showing a strong correlation with the severity of hypertension during pregnancy[39]. The significant association of elevated NT-proBNP levels with adverse outcome supports its potential utility as a prognostic biomarker in clinical risk assessment for pregnant women with PE. Given its widespread use in clinical laboratories, this biomarker may serve as a valuable tool in the management of women with confirmed or suspected PE. Further studies with larger sample sizes are needed to confirm these findings.

Clinical and research implications

Over the past decades, numerous studies have explored the diagnostic and prognostic value of the sFlt-1/PlGF ratio for PE[7–9,37,40]. However, measurement of sFlt-1 and PlGF is not feasible in all laboratories, which restricts the routine application of these biomarkers in clinical practice. In HDP, the maternal cardiovascular system fails to adapt to the increased demands of pregnancy, leading to substantial hypertension-related adverse outcomes[41]. The additional assessment of biochemical cardiovascular parameters seems to improve the prediction of maternal adverse outcomes, offering a window of opportunity

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for intervention to potentially reduce cardiovascular complications in these women. According to our results, NT-proBNP should be considered as a standard parameter for risk assessment for severe maternal adverse outcome in women with HDP.

Strengths and limitations

A key strength of this study is the use of a well-defined and homogeneous cohort. The study provides clinically relevant data regarding the risk of maternal complications associated with PE and gives reference values for maternal serum NT-proBNP levels in this cohort. A limitation of this study is the small sample size, which restricts the ability to establish definitive cut-off values for the biomarkers analyzed. In particular, the relatively small number of events may affect the robustness and generalizability of the multivariable analyses. Given the non-significant result for the sFlt-1/PlGF ratio, further research with larger sample sizes may be warranted to determine if there is truly no association or if this study was underpowered to detect a smaller effect size for this particular biomarker.

Conclusions

In this study, we evaluated the performance of NT-proBNP for the prediction of severe maternal adverse outcome after an established diagnosis of PE. Elevated serum NT-proBNP levels were associated significantly with severe maternal adverse outcome in women with PE, particularly in early-onset cases. NT-proBNP was found to be associated strongly with both severe maternal adverse outcome and time-to-delivery, outperforming the sFlt-1/PlGF ratio in prognostic utility. Given its availability in routine clinical settings and its strong correlation with disease severity, NT-proBNP shows promise as a practical and informative biomarker for risk stratification and surveillance in PE. Before these findings can be translated into clinical practice, prospective validation in larger, independent cohorts is essential to confirm utility and generalizability.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Percentiles for N-terminal pro-B-type natriuretic peptide (NT-proBNP) values in the study cohort.

Table S2 Percentiles for soluble fms-like tyrosine kinase-1 to placental growth factor (sFlt-1/PlGF) ratio values in the study cohort.

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